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Chronic Effects of Neurotrauma Consortium (CENC)

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## Technical Abstract

**Background:** The Chronic Effects of Neurotrauma Consortium (CENC) is a coordinated, multicenter collaboration linking basic science, translational, and clinical neuroscience researchers from the VA, military, and academia to effectively address the diagnostic and therapeutic ramifications of traumatic brain injury (TBI) and its long-term effects. This Consortium is uniquely positioned because of its centralized organization provided by an experienced, professional Coordinating Center directed by senior academic TBI leaders of VA and DOD; 2) linkages between eight major VA TBI/Polytrauma Centers, multiple DoD MTFs, and academic research centers; 3) extensive, long-term track record of collaborative TBI research; 4) access to large military/VA relevant research subject populations, and six innovative and intersecting research projects that are designed to change practice in the near term and lay the groundwork for subsequent investigation. This consortium brings together a nationwide group of researchers who have extensive track records of internal and external collaborations, demonstrated productivity in knowledge translation and dissemination, and the proven ability to recruit and follow up with research subjects.

**Objectives:** The chronic effects from TBIs, whether single or repeated, on chronic disabling symptoms, on recovery from combat and trauma-related comorbidities, and on long-term brain function in veterans and service members are not known. The overarching goals of CENC are to examine the critical issues related to the identification and characterization of the anatomic, molecular and physiological mechanisms of chronic brain injury and potential neurodegeneration. The specific research studies have been designed to directly address the proposed consortium objectives and focus areas, to build on and leverage existing TBI research activities across the network, to provide meaningful answers to the current questions facing individuals and organizations affected by neurotrauma, and to identify and lead a way ahead.

**Research Plan:** (Currently approved studies)

1. A large prospective longitudinal investigation comparing OEF-OIF veterans with combat-related mTBI and non-TBI combat-exposed controls on comprehensive neuropsychological, neuroimaging, genomics, biomarkers, and neuropathology.
2. A basic science project to develop an animal model of repeated mTBI that will allow the tracking of progressive intraneuronal tau alterations that can be correlated with behavioral dysfunction, fluorescent in situ hybridization, and gene expression signatures.
3. A comprehensive analysis of existing VA, DOD and other federal datasets of individuals with TBI and comorbid conditions to facilitate understanding of neurodegeneration epidemiology.
4. A prospective case-controlled study to determine the effect of vestibular dysfunction on balance, gait and quality of life in veterans at the Mountain Home VA Medical Center.
5. A follow up to a prospective case controlled study using advanced MR imaging and clinical outcomes measures 3-5 years after concussive traumatic brain injury (TBI) in US military personnel injured during deployment in which earlier clinical and imaging data exists.
6. A study to facilitate sequence development and pulse programming to guide the interpretation of neuroimaging data from multiple MRI devices.

**Military/VA Benefit:** This project is specifically designed to understand the linkages between blast exposures with TBI, chronic effects, and neurodegeneration to assist in providing current and future care, guide the development of novel interventions to prevent or mitigate cognitive and behavioral decline, and contribute to long-term planning for service member and veteran needs and benefits.

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## **1. INTRODUCTION:**

The mission of the CENC consortium is to fill the gaps in knowledge about the basic science of mild TBI (also termed concussion), to determine its effects on late-life outcomes and neurodegeneration, to identify Service members most susceptible to these effects, and to identify the most effective treatment strategies. The CENC is a multi-center collaboration linking premier basic science, translational, and clinical neuroscience researchers from the DoD, VA, academic universities, and private research institutes to effectively address the scientific, diagnostic, and therapeutic ramifications of mild TBI and its long-term effects.

## **2. KEYWORDS:**

TBI  
Mild-TBI  
Tau  
Blast injuries  
Brain concussion  
Military personnel  
Veterans  
Rehabilitation  
Otolith Dysfunction  
Postural Stability  
Diffusion Tensor Imaging  
OIE/OIF  
Neurosensory

## **3. OVERALL PROJECT SUMMARY:**

For clarity, each principal activity is detailed separately below by key Scope of Work (SOW) domain pertinent to Year 1 activities and requirements.

- I. VCU Coordinating Center: The Coordinating Center at VCU serves both to implement a specific programs of research designed to provide clinically relevant answers and interventions for the current service members (SMs) and Veterans and provides leadership in developing innovative research proposals and programs to define the long-term solutions to the chronic effects of TBI, which specifically address the research gaps highlighted in our proposal. The Coordinating Center at VCU insures the overall functioning of all components of the CENC and will be the primary point of contact to the sponsors. The primary goal of the VCU Coordinating Center is to insure completion of all activities, sponsor required reporting, and compliance for the CENC.

For the current fiscal year, the VCU Coordinating Center:

- a. Established all interagency contracts and subcontracts per the SOW,

- b. Assisted in IRB and IACUC protocol development for the Neuroimaging Core, the Biostatistics, Data Management, and Study Management Core, the Neuropathology Core, CENC0001C Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat Study, CENC0004C Epidemiology of mTBI and Neurosensory Outcomes Study, CENC0005C Tau Modification and Aggregation in Traumatic Brain Injury Study, CENC0008P Otolith Dysfunction and Postural Stability Study, CENC0025P ADAPT/EVOLVE Study, and CENC0039P DTI Phantom Study,
  - c. Received all IRB approvals for CENC0001C Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat Study
  - d. Received all IACUC approvals for CENC0005C Tau Modification and Aggregation in Traumatic Brain Injury Study,
  - e. Completed and submitted all fiscal and regulatory documentation,
  - f. Aided in the development of SOPs and MOPs for the Neuroimaging Core, the Neuropathology Core, CENC0001C Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat Study, CENC0004C Epidemiology of mTBI and Neurosensory Outcomes Study, CENC0005C Tau Modification and Aggregation in Traumatic Brain Injury Study, CENC0008P Otolith Dysfunction and Postural Stability Study, CENC0025P ADAPT/EVOLVE Study, and CENC0039P DTI Phantom Study,
  - g. Hired two new staff members,
  - h. Hosted an annual meeting with consortium personnel and sponsor representatives,
  - i. Hosted all telecommunications between the Consortium members and the sponsors,
  - j. Developed a Consumer Advisory Board and Scientific Advisory Board (GSC Approval pending), and
  - k. Published research and presented on the CENC at a major international military medicine conference (see Sections 6.a.2. and 6.b. below).
- II. Neuroimaging Core: The Neuroimaging Core, located at the Baylor College of Medicine (BCM) and led by Drs. Elisabeth Wilde and Harvey Levin, includes experts from the fields of neuroradiology, neuropsychology, magnetic resonance imaging (MRI) physics, information technology (IT) and computer programming, and statistics. The Core has facilitated sequence development and pulse programming, training and supervision of technologists and support personnel, and quality assurance (QA) in support of CENC. At the time of this report, the Core has:

- a. Assisted in the IRB protocol development, submission, and approvals for CENC0001C Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat Study,
- b. Developed standardization for all CENC MRI scanners and techniques,
- c. Developed its SOP and MOP, and
- d. Trained all personnel on CENC-specific protocols in support of CENC0001C Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat Study.

III. Biostatistics [B], Data Management [DM], and Study Management [SM] Core:

The Biostatistics, Data Management, and Study Management Core (BDMSM) is located at RTI and led by Dr. Rick Williams. The Core serves as a statistics support and study management resource for the CENC and all consortium members. During this fiscal year, the BDMSM Core has:

- a. Developed the CENC website and interactive portal (<https://cenc.rti.org>),
- b. Assisted with the development of the research plans for CENC0001C Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat Study, CENC0004C Epidemiology of mTBI and Neurosensory Outcomes Study, CENC0005C Tau Modification and Aggregation in Traumatic Brain Injury Study, CENC0008P Otolith Dysfunction and Postural Stability Study, CENC0025P ADAPT/EVOLVE Study, and CENC0039P DTI Phantom Study,
- c. Aided in the development of SOPs and MOPs for the Neuroimaging Core, the Neuropathology Core, CENC0001C Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat Study, CENC0004C Epidemiology of mTBI and Neurosensory Outcomes Study, CENC0005C Tau Modification and Aggregation in Traumatic Brain Injury Study, CENC0008P Otolith Dysfunction and Postural Stability Study, CENC0025P ADAPT/EVOLVE Study, and CENC0039P DTI Phantom Study,
- d. Participated in all consortium wide communications and communications with the sponsors,
- e. Assisted in the development of IRB and IACUC submissions for the Neuroimaging Core, the Neuropathology Core, CENC0001C Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat Study, CENC0004C Epidemiology of mTBI and Neurosensory Outcomes Study, CENC0005C Tau Modification and Aggregation in Traumatic Brain Injury Study, CENC0008P Otolith Dysfunction and Postural Stability Study, CENC0025P ADAPT/EVOLVE Study, and CENC0039P DTI Phantom Study, and
- f. Developed a data transfer plan to sponsor requirements.

- IV. Neuropathology Core: The Neuropathology Core is located at USUHS, led by Dr. Daniel Perl, where a new, state-of-the-art brain bank facility within the auspices of the DoD has been established. The Neuropathology Core will manage the collection of brain specimens from participants using an existing national network of dieners and neuropathologists. During this fiscal year, the Core has:
- Developed its IRB proposal, and
  - Developed its SOP and MOP.
- V. Peer Review Program: The Peer Review Program (PRP) is designed to support the development of additional studies within the consortium including demonstration and feasibility studies. Such studies will address focused questions, develop preliminary data, and provide an avenue for new researchers and novel research approaches to contribute to the overall Consortium program of study, as well as studies meant to replace those submitted as Core Studies in our application but which were not approved by the GSC. In addition to providing funding, the PRP provides support in the form of mentorship and resource sharing, as appropriate and needed, via each of the consortia sites. The Consortium's goal is to support up to three demonstration studies by the end of the first year of the grant and three to five others during the remaining 3 years. During this fiscal year, the PRP program:
- Developed its SOP and MOP,
  - Released an initial RFA resulting in 31 applications, two of which have been fully funded (see Sections IX. CENC0008P Otolith Dysfunction and Postural Stability and X. CENC0025P ADAPT/EVOLVE Study (below). An additional three applications are currently in revision as requested by the GSC,
  - Released a second RFA resulting in 189 pre-applications, 29 of which have been selected for full submission, and
  - Provided substantial and on-going mentorship and resource sharing to applicants to the PRP program.
- VI. CENC0001C Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat: This study's goal is to establish a large cohort (880) of former U.S. OEF/OIF/OND combatants who have had at least one mild Traumatic Brain Injury (mTBI), and follow the members of the cohort long-term to assess specific areas of their physical and mental health. Given the unclear role of mTBI(s) on long term health and the frequent co-occurrence of posttraumatic stress disorder (PTSD) in warfighters, the study will include a group of participants (220) who have experienced combat but have not had an mTBI. During this fiscal year, this study has:



- a. Hired personnel (as appropriate) at various CENC sites for the conduct of this study,
  - b. Developed and gained GSC approval of the final protocol for the project,
  - c. Developed its SOP and MOP,
  - d. Developed, submitted, and acquired IRB approvals at each local site and by HRPO,
  - e. Trained all study staff in the administration and scoring techniques of all study measures and assessments, and
  - f. Developed all associated recruitment materials.
  
- VII. CENC0004C Epidemiology of mTBI and Neurosensory Outcomes Study: The primary objective of this project is to integrate and analyze existing VA healthcare data to study the chronic effects of mild traumatic brain injury (mTBI) on neurodegenerative disease and other comorbidities, and the methods to treat and rehabilitate adverse effects of mTBI, in Veterans over time. During this fiscal year this study has:
  - a. Developed and gained GSC approval of the final protocol for the project,
  - b. Developed its SOP and MOP, and
  - c. Submitted and acquired IRB approval for the study.
  
- VIII. CENC0005C Tau Modification and Aggregation in Traumatic Brain Injury Study: The goal of this study is to develop an animal model of repeated mTBI model that will allow the tracking of progressive intraneuronal tau alterations that can be correlated with behavioral dysfunction, fluorescent in situ hybridization, and gene expression signatures. The model could then be used to assess the effects of interventions. The observations made in the animal model will be tested for agreement in soldiers who have died after sustaining repeated mTBI. During this fiscal year, the study has:
  - a. Developed its SOP and MOP,
  - b. Developed, submitted, and obtained IACUC approval from all study sites,
  - c. Acquired study animals and bred an animal colony,
  - d. Finalized the study protocol,
  - e. Engaged in the study procedures with animals per the study plan,
  - f. Began behavioral testing of mice at different time points pre- and post-single mTBI and repetitive mTBI, and
  - g. Began analysis of tissues samples obtained via the protocol.
  
- IX. CENC0008P Otolith Dysfunction and Postural Stability Study: This study was accepted and funded via the CENC PRP program. This research study is part of a long-term goal to establish a unique treatment platform to diagnose, localize, and treat dizziness and imbalance related to inner ear balance issues associated

with mTBI. In the recent wars in Iraq and Afghanistan, many soldiers have been exposed to blasts from IEDs or roadside bombs, and TBI has been called the signature condition of Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) combat Veterans. The objective of the study is to determine the effect of inner ear balance (vestibular) dysfunction on balance, gait and quality of life. The primary function of the inner ear balance function is to keep vision steady when the head is in motion and to maintain balance. Loss of inner ear balance function can result in dizziness and/or imbalance, and individuals with these symptoms are at risk of falling. The incidence of dizziness and imbalance increases in two populations relevant to VA and military healthcare: older individuals and individuals who have suffered a head injury or blast exposure. During this fiscal year, the study has:

- a. Developed its SOP and MOP,
- b. Developed, submitted, and obtained IRB approval, and
- c. Began the study procedures per the protocol.

- X. CENC0025P ADAPT/EVOLVE Study: This study was accepted and funded via the CENC PRP program. The overall goal of this study is to investigate advanced MR imaging and clinical outcome measures of concussive traumatic brain injury (TBI) in US military personnel injured during deployment. As part of previous collaborative efforts, we completed early prospective, longitudinal studies enrolling active-duty US military at 0-7 days, 0-30 days, and 0-90 days post-injury. All subjects met the DoD definition for mild uncomplicated traumatic brain injury. Non-brain injured control (CTL) subjects were also enrolled at each time point for comparison. Early advanced MR imaging and clinical information was collected before these subjects were followed to 6-12 months. At 6-12 months, advanced MR imaging was repeated and a battery of neurological, neuropsychological and psychiatric evaluations were completed. In total, 591 subjects were enrolled through these efforts; 54% TBI, 46% control. This study will re-examine these subjects now 3-5 years post-injury and compare their current clinical and imaging presentation with the previously acquired longitudinal data. During this fiscal year the study has:

- a. Developed its SOP and MOP,
- b. Developed, submitted, and obtained IRB approval,
- c. Began the study procedures per the protocol, and
- d. Enrolled 8 subjects.

- XI. CENC0039P DTI Phantom Study: Diffusion imaging has gained importance in the past decade as a valuable means of depicting white matter injury caused by various disease processes. Diffusion imaging holds particular promise for evaluation of individuals who have experienced traumatic brain injury (TBI)

because damage to white matter pathways is considered to be an important component in the causation of the many types of neurocognitive impairment that can result from TBI. Diffusion imaging can be performed using a number of different imaging techniques, and no single technique is universally recognized as the single best method. As a result, development of large pools of data is hampered by the fact that combining imaging studies obtained by multiple techniques results in an inhomogeneous data set that is difficult to analyze. If diffusion imaging is to be developed as a means to evaluate Veterans with suspected TBI, a uniform type of image acquisition is needed across the different types of imaging systems available within the VA hospital network. To construct such a system, a means is needed to establish exactly how one scanner differs from another (or from itself over the course of time). Then, modification of imaging sequences and, as needed, hardware and software components, can be performed to allow more uniform data acquisition across scanners. This study uses diffusion imaging phantoms to evaluate differences between scanners with the goal of providing acquisition techniques that will allow data to be compared across different patient groups and combined into large data collections. The objective is to provide a means for the many different scanners across the VA hospital system to provide the same imaging answers in a suspected TBI patient. During this fiscal year, this study has:

- a. Developed its SOP and MOP, and
- b. Finalized the study protocol.

**4. KEY RESEARCH ACCOMPLISHMENTS:** Nothing to report.

**5. CONCLUSION:** Nothing to report.

**6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:**

a.

(1) Lay Press: None to report

(2) Peer-Reviewed Scientific Journals:

Cifu DX, Hoke KW, Wetzel PA, Wares JR, Gitchel G, Carne W. Effect of hyperbaric oxygen on eye tracking abnormalities in males after mild traumatic brain injury. *J Rehabil Res Dev* (in press)

Wares JR, Hoke KW, Walker W, Manning-Franke L, Cifu DX, Carne W, Ford-Smith C. Characterizing the effects of mTBI and PTSD on balance impairments in blast-exposed Service Members and Veterans using computerized posturography. Under consideration.

- (3) Invited Articles: None to report  
(4) Abstracts: None to report

b.

West, S.L. & Cifu, D.X. (October, 2014). The Chronic Effects of Neurotrauma Consortium: Studying the Future Effects of Combat-Related Brain Injury Today. Paper presented at the Australasian Military Medicine Association Annual Conference, Sydney, Australia.

**7. INVENTIONS, PATENTS AND LICENSES:** Nothing to report.

**8. REPORTABLE OUTCOMES:** Nothing to report.

**9. OTHER ACHIEVEMENTS:**

Grant Applicant: V81XWH-133-PhTBI-TED

Title: TBI Endpoints Development Award

P.I. Geoffrey Manley, MD, PhD

Submission Date: February 13, 2013

Dr. David Cifu participated in Geoffrey Manley's application for funding

**10. REFERENCES:**

Nothing to report.

**11. APPENDICES:** quad charts sent to CDMRP